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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,747	WANG ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02/09/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-95* is/are pending in the application.

4a) Of the above claim(s) *51 and 63-95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49,50 and 52-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of Group 13, Claims 49-50, 52-62, directed to methods for detecting abnormal cell growth in the uterus by detecting the protein level of Pin1 in a biological sample, in Paper of 02/09/05 is acknowledged and entered.

Claims 49-95 are pending in the instant application and Claims 51, 63-95 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group 13, Claims 49-50, 52-62, directed to methods for detecting abnormal cell growth in the uterus by detecting the protein level of Pin1 in a biological sample are currently under prosecution.

OBJECTION

1. Claim 49-50, 52-62 are objected to, for the use of the language "Pin 1" as the sole means of identifying the claimed protein, because different laboratories may use the same laboratory designations to define completely distinct proteins. Amendment of the claims to include physical and/or functional characteristics of "Pin1" which unambiguously define "Pin 1" is required.

2. Claim 54 is objected to, because claim 54 broadens claim 49 to which claim 54 depends.

It is noted that a difference in the level of Pin-1 encompasses both an elevation and a decrease. Thus claim 54 reads on a method for detecting abnormal cell growth in the uterus, by detecting either an elevation or a decrease in the level of Pin1 protein,

whereas the limitation of detecting a decrease in the level of Pin1 protein is not found in claim 49 to which claim 54 depends .

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 49-50, 52-53, 55-56, 58-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. It seems that by typographic error, Claims 58-61 recite the limitation " the antibody" in claim 55. There is insufficient antecedent basis for this limitation in the claim 55 from which it depends.

In addition, it seems that by typographic error, Claim 62 recites the limitation " the complex" in claim 55. There is insufficient antecedent basis for this limitation in the claim 55 from which it depends.

For the purpose of compact prosecution, it assumed that claims 58-60 and 62 depend on claim 57, and not claim 55.

2. Claims 49-50, 52-53, 55-56 are rejected under 35 U.S.C. 112, second paragraph, because it is not clear in claim 49 that the level of Pin1 is elevated as compared to what.

3. Claim 53 is indefinite, because it is not clear how the test sample isolated from the uterus of claim 49 could be urine, saliva, sputum, phlem, pus, mucus, bone marrow, lymph, tears or brain body fluid, because one would not expect that urine, saliva, sputum, phlem, pus, mucus, bone marrow, lymph, tears or brain body fluid exists in uterus.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 49-50, 52-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 49-50, 52-62 are drawn to:

A method for detecting abnormal growth in a test sample isolated from uterus, comprising detecting the level of Pin1 in a test sample, wherein an elevation or a difference in the level of Pin1, or an elevation of the amount of the complex between an antibody specific for Pin1 and Pin1 protein in the test sample is indicative of abnormal cell growth (claims 49, 54, 57).

The abnormal cell growth is cancer or uterus carcinosarcoma (claims 55-56).

The method of claim 49, wherein the level of Pin1 is a protein level (claim 50).

The method of claim 49, wherein the test sample is a tissue sample (claim 52) or bodily fluid selected from the group consisting of blood, ascites, serum, urine, saliva, sputum, phlem, pus, mucus, bone marrow, lymph, tears or brain body fluid (claim 53).

The method of claim 57, wherein the antibody is a polyclonal or monoclonal antibody, wherein the antibody could be detectably labeled with radioactive, enzymatic, biotinylated or fluorescent label (claims 58-61).

The method of claim 57, wherein the complex is detected by a second antibody, which comprises a detectable label (claim 62).

The specification recites the use of Pin1 antibodies for detecting Pin1 protein as a breast tumor marker and quotes the reference by Lu et al, 1999, Nature, 399: 784-788 (p.37, lines 4-7). The specification discloses that a commercial polyclonal antibody from Oncogene Research Products, MA is used to screen for Pin1 expression in human tissues (p.43, item under "Antibody").

No disclosure of the structure of Pin1 protein is found in the specification.

A. One cannot extrapolate the teaching in the specification to the enablement of the claims, because **one would not know how to make the invention, due to the lack of disclosure in the claims and in the specification the actual sequence structure of Pin1.**

The attempt to incorporate subject matter into this application by reference to publication by Lu et al, 1999, is improper. MPEP 6.19 and 6.19.01 teaches that incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163

(CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973) (see MPEP 6.19 and 6.19.01) .

Further, without the disclosure of the structure of Pin1 protein in the specification, one would not know how to identify and make the Pin1 protein, and to carry out the claimed method.

B. If Applicant could overcome the above 112, first paragraph, claims 49-50, 52-62 are still rejected under 112, first paragraph, because the claims encompass a method for facilitating the diagnosis of cancer in a subject, or a method for identifying metastatic prostate cancer, comprising assessing the level of "variants" of Pin1 wild type protein in a biological sample.

The specification discloses that the Pin1 markers (e.g. Pin1 nucleic acid molecule, Pin1 protein, Pin1 protein "homologues" and/or Pin1 antibodies) could be used in one or more methods related to Pin1-associated disorders, including diagnosis assays, monitoring clinical trials (p. 10, third paragraph before last, under Uses and Methods of the invention).

The specification appears to include homologues or antibodies as Pin1.

Thus Pin1 encompasses variant or homologue Pin1 protein, and wild type Pin1 protein.

One cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the Pin1 variants would have properties related to that of wild type Pin1 and would have an elevated level of protein in uterus cancer. Schmid S et al, 2001, J comparative Neurology, 430(2): 160-71, teach that the variants

flip/flop of the gene GluR are expressed at higher levels in neurons in the auditory braistem, as compared to the wild type GluR-A and GluR-B, and that neurons in the central nucleus of the inferior collicullus express high levels of GluR-B flip but only low levels of the other receptor subunits. Conner et al, 1996, Mol Brain Res, 42: 1-17, teach that full length trkB is found the hippocampus in patients with Alzheimer's disease, but not in hippocampi of either normal age-matched individual or patients with Huntington's disease, and that truncated trkB is found in senile plaques in hippocampus and temporal lobe in both patients with Alzheimer's disease and Huntington's disease, but not in normal brains of aged-matched individuals (page 8, item 3.1.2).

The specification does not disclose how to make the claimed Pin1 variants, such that they would function or have the properties as claimed, or how to use said Pin1 variants if they did not have the function or properties claimed.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

C. If Applicant could overcome the above 112, first paragraph, claims 49-50, 52-54, 57-62 are still rejected under 112, first paragraph for lack of enablement for a method for detecting abnormal cell growth.

The specification discloses that Pin1 protein is overexpressed in cancer of uterine cervix, and endometrium tissues, or cervical carcinoma, and carcinosarcoma of the uterus, and that in normal tissues, the Pin1 protein level is low, except for normal kidney, brain, pancreatic islet cells and testis tissues (Example 6, especially table 1 on page 44, and the table on page 52).

The specification also discloses that as used here, abnormal cell growth is intended to include cell growth that is undesirable or inappropriate, and that abnormal cell growth can be benign (p.11, second paragraph).

It is noted that the definition is not limiting, and that abnormal cellular growth encompasses any growth of cells, provided it is undesirable or inappropriate, i.e. any abnormal formation of tissue, as a tumor or growth, and is not necessarily cancerous growth, for example, a benign tumor, a histoid, a multicentric, or an organoid (Taber's cyclopedic medical dictionary, 16th ed, 1989, pages 1190-1191).

One cannot extrapolate the teaching of the specification to the scope of the claims because different diseases have different etiology, and expression of a gene in certain diseases is unrelated to its expression in other diseases, and thus it is unpredictable that over-expression of Pin1 protein is found in any abnormal cellular growth, such as a benign tumor, a histoid, a multicentric, or an organoid.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

D. If Applicant could overcome the above 112, first paragraph rejection, claims 49, 52-56 are still rejected under 112, first paragraph, for lack of enablement for a method for detecting abnormal cell growth or cancer of the uterus, by detecting the Pin1 level, which reads on "the mRNA level of Pin1 polynucleotide, or the level of Pin1 antibody".

It is noted "the level of Pin1" as cited in claims 49, 52-56 encompasses the mRNA level of Pin1 polynucleotide, or of Pin1 antibody, in view that the specification discloses

that the Pin1 markers (e.g. Pin1 nucleic acid molecule, Pin1 protein, Pin1 protein homologues and/or Pin1 antibodies) could be used in one or more methods related to Pin1-associated disorders, including diagnosis assays, monitoring clinical trials (p. 10, third paragraph before last, under Uses and Methods of the invention).

It is further noted that the specification only discloses the overexpression of Pin1 protein, as detected by anti-Pin1 antibodies, in cancer.

One cannot extrapolate from the overexpression of Pin1 protein in uterus cancer to the overexpression of mRNAs of Pin1 polypeptide in uterus cancer, because one cannot predict that protein levels are correlated with steady-state mRNA levels or alterations in mRNA levels. For instance, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Yokota, J et al (Oncogene, 1988,Vol.3, pp. 471-475) teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels,

suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-translational level. Thus, the mRNA expression level cannot be predicted from the level of encoded protein, due to the multitude of homeostatic factors affecting transcription and translation.

Further, one cannot extrapolate from the overexpression of Pin1 protein in patients having uterus cancer to the overexpression of antibodies specific for Pin1 polypeptide in patients having uterus cancer, because there is no indication that patients having uterus cancer produce detectable elevated level of autoantibodies specific for Pin1 polypeptide. Boon (Adv Can Res, 1992, 58:177-210) teaches that establishment of immune tolerance may occur and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, due to possible inconsistencies in antigen expression or presentation by tumor cells (Boon et al, p.178, paragraph before last paragraph), one cannot predict that autoantibodies against Pin1 protein could be detected in patients with uterus cancer. There is however no indication in the specification that the expression of the Pin1 antigens has resulted in autoantibodies against the Pin1 antigen.

In view of the above, one of skill in he art would be forced into undue to practice the claimed invention.

E. If Applicant could overcome the above 112, first paragraph rejection, claims 54 is still rejected under 112, first paragraph, for lack of enablement for a

method for detecting abnormal cell growth or cancer of the uterus, by detecting "a difference" in the level of Pin1.

It is noted a difference in the level of Pin1 protein in uterus cancer encompasses an increase or a decrease in the level of Pin1 protein in uterus cancer.

The specification discloses that the level of Pin1 protein increases in uterus cancer as compared to that of normal control tissue, supra.

There is however no indication that the level of Pin1 protein also decreases in uterus cancer.

In view of the above, one of skill in he art would be forced into undue to practice the claimed invention.

F. **If Applicant could overcome the above 112, first paragraph rejection, claims 53 is still rejected under 112, first paragraph, for lack of enablement for a method for detecting abnormal cell growth of the uterus, by detecting the level of Pin1 in a test sample which is urine, saliva, sputum, phlem, pus, mucus, bone marrow, lymph, tears or brain body fluid.**

It is not clear how the test sample isolated from the uterus of claim 49 could be urine, saliva, sputum, phlem, pus, mucus, bone marrow, lymph, tears or brain body fluid, because one would not expect that urine, saliva, sputum, phlem, pus, mucus, bone marrow, lymph, tears or brain body fluid exists in uterus.

In view of the above, one of skill in he art would be forced into undue to practice the claimed invention.

REJECTION UNDER 35 USC 102(e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 49-50, 52-55, 57-62 are rejected under 35 U.S.C. 102(e) as being anticipated by Lu et al (US20020025521 A1).

Claims 49-50, 52-55, 57-62 are drawn to:

A method for detecting abnormal growth in a test sample isolated from uterus, comprising detecting the level of Pin1 in a test sample, wherein an elevation or a difference in the level of Pin1, or an elevation of the amount of the complex between an antibody specific for Pin1 and Pin1 protein in the test sample is indicative of abnormal cell growth (claims 49, 54, 57).

The abnormal cell growth is cancer (claim 55).

The method of claim 49, wherein the level of Pin1 is a protein level (claim 50).

The method of claim 49, wherein the test sample is a tissue sample (claim 52) or a bodily fluid which is ascites (claim 53).

The method of claim 55, wherein the antibody is a polyclonal or monoclonal antibody, wherein the antibody could be detectably labeled with radioactive, enzymatic, biotinylated or fluorescent label (claims 58-61).

The method of claim 55, wherein the complex is detected by a second antibody, which comprises a detectable label (claim 62).

For the purpose of compact prosecution, it is assumed that claims 58-62 are dependent on claim 57, and not claim 55.

Lu et al teach a method for detecting abnormal cell growth or cervical cancer, comprising assessing the level of Pin1 in a test sample, wherein an elevation or a difference in the levels of Pin1 is indicative of abnormal cell growth claims (1, 8, 10, 14). Lu et al teach that the level of Pin1 protein is detected by antibody specific for Pin1 (Claims 16, 20). Lu et al teach that the test sample includes sample obtained from tissue (page 14, second column 14, para 0125), or a bodily fluid which is ascites (claim 5). Lu et al teach that the antibody is a polyclonal or monoclonal antibody, wherein the antibody could be detectably labeled with radioactive, enzymatic, biotinylated or fluorescent label, and that the complex between the antibody and Pin1 is detected by a second antibody, which comprises a detectable label (claims 17, 18, 22-24).

It is noted that cervix cancer is part of the uterus cancer (uterine cervix cancer), as shown by Masferrer, JL et al (US20040122011 A1).

Although the reference does not specifically teach a method for detecting cancer of the uterus, however, the claimed method appears to be the same as the prior art method. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

May 12, 2005

SUSAN UNGAR, PH.D
PRIMARY EXAMINER